Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 57, No. 16, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.01.015

STATE-OF-THE-ART PAPER

Update 2011: Clinical and Genetic Issues in Familial Dilated Cardiomyopathy

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A great deal of progress has recently been made in the discovery and understanding of the genetics of familial dilated cardiomyopathy (FDC). A consensus has emerged that with a new diagnosis of idiopathic dilated cardiomyopathy (IDC), the clinical screening of first-degree family members will reveal FDC in at least 20% to 35% of those family members. Point mutations in 31 autosomal and 2 X-linked genes representing diverse gene ontogeny have been implicated in causing FDC but account for only 30% to 35% of genetic causes. Next-generation sequencing methods have dramatically decreased sequencing costs, making clinical genetic testing feasible for extensive panels of dilated cardiomyopathy genes. Next-generation sequencing also provides opportunities to discover additional genetic causes of FDC and IDC. Guidelines for evaluation and testing of FDC and IDC are now available, and when combined with FDC genetic testing and counseling, will bring FDC/IDC genetics to the forefront of cardiovascular genetic medicine. (J Am Coll Cardiol 2011;57:1641–9) © 2011 by the American College of Cardiology Foundation

Since our 2005 review of familial dilated cardiomyopathy (FDC) genetics (1), a great deal of additional progress has been made. We have noted other valuable dilated cardiomyopathy (DCM) reviews, consensus documents, and guidelines since 2005 (2–17). We will review key concepts of genetic research and provide recent updates in FDC genetics. We also will review the dramatic innovations in sequencing technologies that are revolutionizing clinical and research genetic studies. Much of this information is broadly applicable to all of cardiovascular genetics.

Background: Genetic Studies, Phenotype, and Genotype

Phenotype studies. In our previous review (1), we cited 19 DCM phenotype studies published between 1981 and 2003, principally focused on estimating the fraction of those patients with idiopathic dilated cardiomyopathy (IDC) who were found to have FDC using family history (FH) or clinical screening of family members. Familial dilated cardiomyopathy is defined most conservatively as DCM meeting criteria for IDC in at least 2 closely related family members (1). Large retrospective studies in the 1980s estimated that 2% to 10% of individuals with IDC had FDC. In the 1990s, studies involving larger cohorts of patients with IDC and prospective cardiovascular screening in their close relatives estimated that 20% to 48% of individuals with IDC could be shown to have FDC (18–20). A consensus has emerged that FDC will be found in at least 20% to 35% of those with IDC with clinical screening of first-degree family members, when clinical screening includes electrocardiogram and echocardiography or some other measure of left ventricle size and function. Notably, a family history without clinical screening is much less sensitive to detect FDC (18).

Genetics studies. In 2005, we listed 19 genes shown to cause nonsyndromic DCM in humans (1). We now list 33 genes, 31 autosomal and 2 X-linked (Table 1) (21–83), associated with DCM covering significant gene ontogeny (Table 2). Notably, the frequencies of DCM mutations in any 1 gene are low (<1% to 6% to 8%), and a genetic cause is identified in only 30% to 35% of FDC cases (Table 1). In contrast, in hypertrophic cardiomyopathy (HCM), a genetic cause can be found in 50% to 75% of familial cases; in those patients for which a mutation is identified, more than 80% can be found in 1 of 2 genes (myosin heavy chain 7, myosin-binding protein C) (13). By inference from HCM (and long QT syndrome [LQTS] and arrhythmogenic right ventricular dysplasia [ARVD/C] [13,16]), FDC genetics are inherently more complex.

The number of DCM genes will continue to increase with ongoing discovery efforts. Also, "crossover" DCM phenotypes of desmosomal genes usually associated with ARVD/C present as DCM with low frequency (84); DCM phenotypes have also been observed for genes principally observed in HCM or LQTS, as previously

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Manuscript received September 8, 2010; revised manuscript received December 27, 2010, accepted January 31, 2011.

JACC Vol. 57, No. 16, 2011
April 19, 2011:1641–9

Abbreviations and Acronyms

ARVD/C = arrhythmogenic right ventricular dysplasia

DCM = dilated cardiomyopathy

FDC = familial dilated cardiomyopathy

FH = family history

HCM = hypertrophic cardiomyopathy

IDC = idiopathic dilated cardiomyopathy

LQTS = long QT syndrome

NGS = next-generation sequencing

WGS = whole-genome sequencing

reviewed (12,13). We and others have recently shown that rare variant genetics are at play in some cases of peripartum cardiomyopathy (85–87).

What Has Not Changed Over the Past 5 Years?

The core approach to human genetic studies remains the same: the careful and comprehensive phenotyping of patients and their family members and then correlating those phenotypes with genetic information. The challenge of this approach is to assure oneself that the genetic variation identified is causative of the phenotype of interest.

Gene mutations. The term "mutation" is most commonly applied in Mendelian disease to one or a short string of variants in coding DNA (Table 3). The most common are missense mutations, but less common types include nonsense, splice site, and short insertion or deletion mutations (Table 3). Synonymous variants do not change the amino acid of the codon, whereas nonsynonymous variants do change the amino acid of the codon.

Classifying variants as disease-causing mutations. Ascertaining whether any one specific variant is causing the phenotype of interest requires weighing of several types of evidence, and achieving a high level of certainty for any one variant is challenging, especially if that variant is novel (Table 3) (1,88–90). In most cases, the sum of all of the evidence is required to decide if the identified variants are relevant (Table 3). As noted in the following, with next-generation sequencing (NGS) approaches, unique genetic variants identified in an individual affected with a specific phenotype can be many—hundreds to thousands—creating new challenges.

Phenotypic considerations. The term "Mendelian disease" has been applied to heritable genetic diseases, usually familial, with identifiable inheritance patterns (dominant or recessive, and autosomal, X-linked, or mitochondrial) (1). Many Mendelian diseases are uncommon to rare, with population frequencies well below 1%. For Mendelian diseases demonstrating autosomal dominant inheritance (which is the case in most families with FDC) (1), the most powerful evidence that a putative mutation is indeed disease causing is segregation of the variant of interest with the disease phenotype in at least 1 large, multigenerational family with multiple affected individuals who carry the variant and multiple unaffected individuals who do not carry the variant (Table 3). Multiple large families available to assess segregation increases the strength of evidence. Although this concept is superficially simple, certain features of adult-onset Mendelian disease commonly observed with FDC complicate this approach.

One feature is incomplete penetrance, which refers to individuals who carry a mutation but do not manifest any evidence of the disease phenotype. Thus, in gene discovery studies, the absence of a DCM phenotype in someone carrying a putative disease-causing variant can never be considered absolute evidence that the variant is not relevant: the individual in question may simply be manifesting incomplete penetrance. A key corollary for clinicians caring for at-risk family members is that a negative clinical cardiovascular evaluation at any age does not rule out the possibility that the family member may develop later disease. This provides the rationale for the periodic rescreening of at-risk family members who have normal evaluations.

A related concept, age-dependent or age-related penetrance, is also observed with FDC, in which a disease-causing mutation usually manifests a disease phenotype only in the adult years, most commonly in the fourth to sixth decades or later.

Another feature that complicates FDC assessment is variable expressivity, which means that only some aspects of the DCM phenotype are present. For example, only mild left ventricular enlargement without systolic dysfunction or the onset of arrhythmia or conduction system disease with only borderline DCM may be observed. Also, age of onset can vary significantly, with variable severity of disease progression. Thus, within a large family with FDC, a wide range of clinical findings may be present, without fully developed DCM. Reliance on endophenotypes (partial phenotypes or subphenotypes) as an indication of genetic DCM/FDC also has been problematic, in part because subtle clinical changes may result from other more common causes of cardiovascular disease, making it difficult to decipher genetic from nongenetic cause.

Although usually nonsyndromic, DCM can be included in syndromic disease involving various organ systems, most commonly skeletal muscle disease (muscular dystrophy) (12).

Genotype considerations. Other criteria to assign causality (Table 3), in addition to segregation of the variant with the phenotype, include the phenotype's relative rarity in control DNA (commonly <1%). The rationale for this is that if it were common in the population, it would be unlikely to cause a rare genetic disease. Nevertheless, how rare is rare (<0.01, <0.005, <0.001, <0.0001)? Some analyses have suggested that the majority of rare alleles (0.001 to 0.003) may be injurious (91). The caveat with control DNA is that it should be representative of the race and/or ethnicity of the family with DCM because variants observed to be common (>1%) in one population can be rare in a different population.

Conservation of the amino acid or nucleotide (i.e., lack of variation in the protein structure or specific nucleotide sequence [92,93] of lower species) is also used to assess

Table 1 Genes Reported in Association With Nonsyndromic DCM*

Gene†	Protein	Function	OMIM	Estimated Fraction of DCM†	Ref. #
LMNA	Lamin A/C	Structure/stability of inner nuclear membrane; gene expression	150330	0.06	21–33
MYH6	Alpha-myosin heavy chain	Sarcomeric protein; muscle contraction	160710	0.043	34,35
MYH7	Beta-myosin heavy chain	Sarcomeric protein; muscle contraction	160760	0.042	36–39
MYPN	Myopalladin	Sarcomeric protein; Z-disc	608517	0.035	40
TNNT2	Cardiac troponin T	Sarcomeric protein; muscle contraction	191045	0.029	36,38,39,41–44
SCN5A	Sodium channel	Controls sodium ion flux	600163	0.026	39,45,46
MYBPC3	Myosin-binding protein C	Sarcomeric protein; muscle contraction	600958	0.02	35,37
RBM20	RNA-binding protein 20	RNA-binding protein of spliceosome		0.019	
TMPO	Thymopoietin	Also LAP2, a lamin-associated nuclear protein	188380	0.011	47
LAMA4	Laminin alpha 4	Extracellular matrix protein	600133	0.011	48
VCL	Metavinculin	Sarcomere structure; intercalated discs	193065	0.01	38,49
LDB3	LIM domain-binding 3; cypher; Z-band alternatively spliced PDZ motif-containing protein	Cytoskeletal assembly; clustering of membrane proteins	605906	0.01	39,50
TCAP	Titin-cap; telethonin	Z-disc protein that associates with titin; sarcomere assembly	604488	0.01	39,51
PSEN1/2	Presenilin 1/2	Transmembrane proteins; gamma secretase activity	104311/600759	0.01	52
ACTN2	Alpha-actinin 2	Sarcomere structure; anchor for myofibrillar actin	102573	0.009	53
CRYAB	Alpha B crystallin	Cytoskeletal protein	123590	0.007	54
TPM1	Alpha-tropomyosin	Sarcomeric protein; muscle contraction	191010	0.006	35,55,56
ABCC9	Sulfonylurea receptor 2A	Kir6.2 regulatory subunit; inwardly rectifying cardiac potassium ATP channel	601439	0.006	57
ACTC	Cardiac actin	Sarcomeric protein; muscle contraction	102540	0.005	58–63
PDLIM3	PDZ LIM domain protein 3	Cytoskeletal protein	605889	0.005	64
ILK	Integrin-linked kinase	Intracellular serine-threonine kinase; interacts with integrins	602366	0.005	48
TNNC1	Cardiac troponin C	Sarcomeric protein; muscle contraction	191040	0.004	35,43
TNNI3	Cardiac troponin I	Sarcomeric protein, muscle contraction; also seen as recessive	191044	0.004	35,65,66
PLN	Phospholamban	Sarcoplasmic reticulum calcium regulator; inhibits sarco/endoplasmic reticulum calcium-ATPase pump	172405	0.004	38,67–70
DES	Desmin	DAGC; transduces contractile forces	125660	0.003	61,71,72
SGCD	Delta-sarcoglycan	DAGC; transduces contractile forces	601411	0.003	72–74
CSRP3	Cysteine- and glycine-rich protein 3; muscle LIM protein	Sarcomere stretch sensor/Z-discs	600824	0.003	39,75
TTN	Titin	Sarcomere structure/extensible scaffold for other proteins	188840	N/A	76,77
EYA4	Eyes absent 4	Transcriptional coactivator	603550	N/A	78
ANKRD1	Ankyrin repeat domain-containing protein 1	Cardiac ankyrin repeat protein; localized to myopalladin/titin complex	609599	N/A	79
DMD‡	Dystrophin	DAGC; transduces contractile force	300377	N/A	80,81
TAZ/G4.5‡	Tafazzin	Unknown	300394	N/A	82,83

*See reference 12 for dilated cardiomyopathy (DCM) associated with syndromic disease and reference 15 for genes not listed here that routinely cause combined skeletal and cardiac myopathies. †Genes ordered by estimates of the fraction of DCM probands carrying mutations from primary and secondary reports; all are autosomal except as indicated. ‡X-linked genes.
DAGC = dystrophin-associated glycoprotein complex; N/A = not available (inadequate data for estimate); OMIM = Online Mendelian Inheritance in Man.

variants, with the rationale that an amino acid or a nucleotide position with greater variation in lower species may have increased tolerance to variants at that position and is therefore less likely to be disease causing. Other features are also relevant (Table 3).

Much of this information, vital for discovery efforts, is also relevant for FDC clinical genetics. These fundamental principles of human genetics investigations have not changed; however, with NGS, the quantity of data to which they are applied has changed dramatically.

Genetic counseling. Text limitations do not permit a reiteration of the components and importance of skilled genetic counseling, especially for difficult, confusing, or syndromic cases, supported by geneticist consultations as needed (1). Unlike most cardiologists, genetic counselors are trained to deal with the family as a unit of inquiry rather

Table 2 Dilated Cardiomyopathy Gene Ontology

Sarcomere	Z-Disc	Cytoskeleton	Mitochondrial	RNA Binding	Ion Channel	Gamma Secretase Activity	Sarcoplasmic Reticulum	Transcription Factor	Nuclear Envelope
ACTC	*TCAP*	*DMD*	*TAZ/G4.5*	*RBM20*	*ABCC*	*PSEN1*	*PLN*	*EYA4*	*LMNA*
MYH7	*CSRP3*	*DES*			*SCN5A*	*PSEN2*			*TMPO*
MYH6	*ACTN2*	*LDB3*							
MYBPC3	*MYPN*	*SGCD*							
TNNT2	*ANKRD1*	*PDLIM3*							
TNNC1		*VCL*							
TNNI3		*RYAB*							
TPM1		*ILK*							
TTN		*LAMA4*							

Table 3 Considerations for Molecular Genetic Testing

A. Types of molecular genetic variants*	**Comment**
Affects exonic (coding) sequences	
Missense	Single-base variant that changes amino acid
Nonsense	Single-base variant that changes amino acid to stop codon
Insertion/deletion (indel)	Usually ≥1 nucleotide(s) inserted or deleted; unless indel is in a multiple of 3, a frameshift occurs that garbles usual amino acid sequence, usually resulting in eventual stop codon
Affects intronic or splice site sequences	
Splice site	Affects exon splicing; ≥1 exons may be skipped
Intronic	Intronic sequencing is noncoding; although intronic variation is more common than coding sequence, it is infrequently associated with disease
B. Testing categories of sequence variations relevant to phenotype of interest (90)	
Sequence variation has been previously reported and is recognized cause of disorder	
Sequence variation has been previously unreported and is of type expected to cause disorder	
Sequence variation has been previously unreported and is of type that may or may not be causative of disorder (also commonly referred to as variant of unknown significance)	
Sequence variation has been previously unreported and is probably not causative of disease	
Sequence variation has been previously reported and is recognized neutral variant	
Sequence variation is not known or expected to be causative of disease but is found to be associated with clinical presentation	
C. Criteria used to assess relevance of genetic variant for phenotype of interest	
Property	**Comment**
Prior molecular genetic diagnostic classification, if available	May be definitive for variants previously established as disease causing
Type of variant (see section A of this table)	Synonymous variant only in unusual circumstances is considered relevant for disease (e.g., variant that opens cryptic splice acceptor site)
Weight of evidence, in the gene in question, that rare nonsynonymous variants cause DCM	†See comment below
Disruption of a functional protein in the tissue of interest that could lead to plausible pathophysiology	Examples of established genes include those encoding proteins of contractile apparatus (see Table 1). This is especially relevant for a novel gene under consideration in a discovery study. For discovery studies, evidence of cardiac expression or the presence of the protein product in cardiac tissue may aid in assessing relevance
Rarity in population	Many Mendelian variants may be "private" or unique to proband or family
Variant segregates with DCM phenotype, ideally in ≥1 large families; lacking large families, variant segregates with DCM in multiple smaller families or is observed in multiple patients with sporadic DCM	In genetic DCM (and other multilocus Mendelian diseases), many variants are "private" so that multiple probands or families with any 1 specific variant are uncommon
Functional data derived from variant: cellular or animal models that recapitulate the disease phenotype	All model systems have inherent limitations and seldom provide definitive studies; however, such functional data increase certainty that the variant under study is relevant for the phenotype of interest

*These variants do not account for copy number variants (CNVs; also termed structural variants), which are insertions, deletions, duplications, or inversions of larger portions of DNA. CNVs range widely in size, from very small (<100 nucleotides) to very large (many megabases), with all sizes in between. They may affect both coding and noncoding DNA. Structural variants are not detected by usual sequencing approaches. Systematic evaluation of structural variants has not been undertaken in dilated cardiomyopathy (DCM), and hence, their relevance for DCM has not been established. †Some genes (e.g., *LMNA, MYH7, TNNT2*; see Table 1) have abundant evidence that point mutations can cause DCM. Nevertheless, because of the marked allelic heterogeneity in DCM genes, it is uncommon for any 1 specific variant to be found in multiple unrelated probands, even in these genes. Whether any of these novel nonsynonymous rare variants can be considered disease causing by usual molecular genetic diagnostic standards is an open question. Further, because most of the DCM genes (Table 1) have had only a few reported pathologic variants, newly identified rare variants in such genes with fewer prior DCM sequencing data available are commonly reported as variants of unknown significance (section B of this table).

than the individual patient, an essential quality for genetic medicine. Genetic counselors are also trained to emphasize disease prevention in contrast to the focus on disease treatment taken by most cardiovascular specialists. Both of these qualities are particularly relevant for facilitating genetic risk assessment. The availability of genetic counselors with cardiovascular training or experience can provide the support needed to initiate the practice of cardiovascular genetic medicine. Several articles deal with these important points (1,12,15,16,94–96).

What Has Changed Over the Past 5 Years?

Sequencing methods. The most significant change is the dramatic improvement in efficiency and speed of gene sequencing methods. Next-generation sequencing is the term used to describe several diverse methods that improve sequencing throughput by several magnitudes, resulting in markedly reduced sequencing costs per nucleotide. This has led recently to sequencing the human exome routinely for research applications (97–99). The exome is defined as the protein-coding portion (exons) of the 18,000 to 19,000 genes, estimated at 1% to 2% of the human genome. Next-generation sequencing is also used to sequence the entire human genome (coding and noncoding regions of DNA), referred to as whole-genome sequencing (WGS) (100). Because Mendelian disease typically affects the protein-coding portions of the genome, exome sequencing is particularly relevant for rare-variant Mendelian disease. As of 2010, typical costs of exome sequencing for research purposes are approximately $2,000 per DNA sample. New instruments and new methods for multiplexing DNA on NGS instruments are being developed that will improve throughput and decrease cost, making <$1,000, or even <$500, exome sequences likely in the near future. Whole-genome sequencing charges on the open market now range from $10,000 to $20,000; these costs are also expected to decrease dramatically (10- to 20-fold) in the next few years, which will bring even WGS into the realm of clinical genetic testing, as well as within the domain of the National Institutes of Health research budgets of many cardiovascular genetics studies. Next-generation sequencing, whether for exome sequencing or WGS, is dramatically transforming the experimental possibilities—study designs unthinkable even 1 to 2 years ago can now be proposed and completed (97–99).

Along with this rapidly expanding universe of opportunity from NGS will come monstrous quantities of human DNA sequence data, challenging the hardware and software of informatics platforms and necessitating novel approaches to data assembly, storage, and analysis. Computational budgets for even modest exome projects (terabytes of data) now cost tens of thousands of dollars; larger projects containing hundreds to thousands of terabytes of data will require more robust outlays. These realities will require new "pipelines" to be developed to efficiently analyze these massive datasets and reduce the cost of storage. This will also require new control DNA datasets to be generated, some of which are now underway (101).

Impact of NGS on clinical molecular genetic testing. Next-generation sequencing is directly related to the emergence of clinical genetic testing for FDC. As recently as 2 to 3 years ago, clinical genetic testing costing thousands of dollars was available only for a few HCM genes. Now panels of dozens of genes at reduced cost, incorporating many or all reported for any of the genetic cardiomyopathies (DCM, HCM, restrictive cardiomyopathy, ARVD/C, and left ventricular noncompaction), are rapidly emerging using NGS methods. Although this increase in data comes with a host of limitations and complications in interpretation, FDC testing sensitivity (the probability of finding a genetic cause with the genetic testing) now ranges from 15% to 25%, making pre-symptomatic testing feasible. Testing laboratories for DCM genes are catalogued at GeneTests (102), an online service hosted by the National Center for Biotechnology Information.

The Genetic Information Nondiscrimination Act of 2008. After many years of effort, a new federal law called the Genetic Information Nondiscrimination Act now protects individuals from genetic discrimination in health care or employment. Further information is available at the National Genome Research Institute website (103).

Ongoing Issues

Clinical progress. Despite the evidence supporting a genetic basis of IDC/FDC, the implementation of guidelines (13) by practitioners has been tepid. Adherence to such guidelines will require a shift in focus from strictly therapeutic measures for a single patient presenting with advanced disease to the consideration and assessment of DCM risk for an entire family (Fig. 1) (1,13,16).

The rationale for these recommendations is that most IDC/DCM presents late in its causal pathway (advanced disease, usually with heart failure or sudden cardiac death), but early detection of asymptomatic DCM through screening enables presymptomatic intervention that may prevent or ameliorate the progression to advanced disease (95).

With a new IDC diagnosis, genetic risk evaluation should be initiated, including taking a 3- to 4-generation family history and recommending that first-degree family members undergo clinical cardiovascular screening (Fig. 1). Clinical genetic testing may also be warranted, including the competent interpretation of genetic results with appropriate counseling (1,16). All of this may require referral of patients to centers providing expertise in cardiovascular genetics and guidance on implementation of gene- and/or mutation-specific therapies if indicated (13), ideally in centers with geneticists or genetic counselors working in collaboration with cardiologists (95).

JACC Vol. 57, No. 16, 2011
April 19, 2011:1641–9

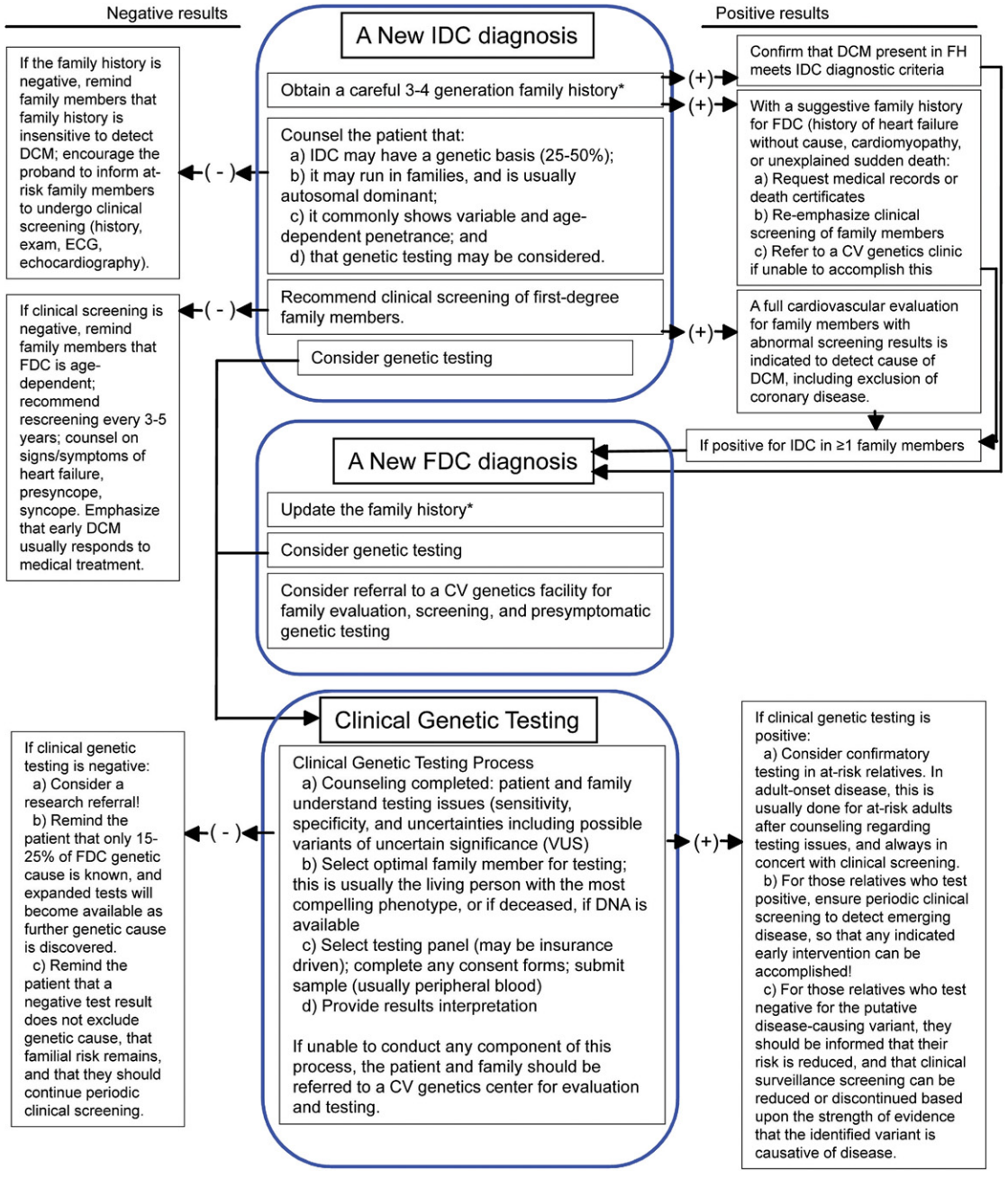

Figure 1 **Flow Diagram of Genetic Risk Assessment for Patients Newly Diagnosed With IDC or FDC**

The boxes on the left and right provide guidance for negative or positive results, respectively, based on the results of history or testing recommended in the central boxes. *Always search for history or examination findings consistent with syndromic disease, particularly skeletal muscle symptoms. However, with any suggestion of syndromic disease in the proband or family members, strongly consider referral to a geneticist or cardiovascular (CV) genetic medicine clinic with genetics collaboration. Some features of early onset conduction system disease or arrhythmia (usually from lamin A/C rare variants) may be particularly susceptible to genetic testing. Rare variants of unknown significance are not helpful for predictive testing. DCM = dilated cardiomyopathy; ECG = electrocardiogram; FDC = familial dilated cardiomyopathy; FH = family history; IDC = idiopathic dilated cardiomyopathy.

How many genes might be involved in DCM? Even though rare variants have been identified for more than 30 genes, we estimate that this accounts for only one-third of genetic causes of FDC. We predict that this number will expand significantly. Discovery of additional genetic causes of DCM is still key to further understanding DCM genetics.

Genetic model for DCM. We have only scratched the surface in understanding DCM genetics. We have almost no insight into the causes of the marked variation in age of

onset, disease penetrance, or clinical severity observed even for the same mutation within a large extended family or between families with the same variant. Gene-environment interactions may explain some of the variability, but additional genetic variation may also explain a portion. Most of the FDC genetic data thus far support a 1-gene Mendelian model with marked locus (many genes) and marked allelic heterogeneity (many private mutations within any one gene). The impact of multiple mutations in the same individual has been recognized for HCM (104–109) and LQTS (108,110), for which 2 or more mutations have been shown to be associated with earlier onset and more severe disease in 3% to 7% of patients. However, considerable additional genetic variation may be at play. Such genetic variation could include "less common" common variants (e.g., allele frequencies of 0.5% to 5%), additional rare variants (including the biallelic models as shown in HCM and ARVD/C [111,112]), epigenetic factors, gene promoter site variants, or alterations in other genetically driven regulatory processes such as microRNAs or their target sites. All of these potential variations remain to be evaluated for genetic DCM.

Is IDC a genetic disease? A related issue involves the genetics of IDC, or DCM after all known causes (except genetic) have been ruled out, and its relationship to FDC. This issue is important because understanding the genetic basis of IDC could have a major public health impact, as nonischemic DCM makes up a significant proportion of all forms of cardiomyopathy and IDC is by far the largest component of nonischemic DCM. Here we differentiate "true" IDC as a patient with IDC who has had their first-degree family members clinically screened (history, examination, echocardiogram, electrocardiogram) to rule out FDC versus a "presumptive" IDC—one who is negative for familial disease by a careful 3- to 4-generation family history but has not had family members screened beyond the FH. Preliminary data from our resequencing studies have suggested that the frequency of possibly or likely disease-causing rare variants in a cohort of FDC and IDC probands (>300 in total) was similar (35,39). However, in those studies, the family members of the IDC probands were not systematically screened beyond FH, making it difficult to accurately assess the familial nature of disease in the "apparently sporadic" IDC portion of our cohort. Therefore, whether "true" sporadic IDC differs from FDC in gene composition, penetrance, or expressivity remains untested in a large prospective study.

Summary

Recent progress for DCM genetics has been significant, although much remains to be learned. Clinical genetic testing is rapidly emerging, and NGS technology now permits patients to undergo clinical genetic testing for many genes at reduced cost. However, enthusiasm for DCM genetic testing remains tempered in 2011 in large part because of the testing sensitivity of 15% to 25% and the plethora of DCM genes that make the rare variants "established as disease causing" in any one gene only a very few. The discovery of new DCM genes and other DCM genetic causes, accelerated now by exome sequencing and soon by WGS, will lead to knowledge of the remainder of the genetic makeup of FDC and IDC. The careful and systematic phenotyping of DCM (whether sporadic or familial) probands and family members, when combined with the cataloging of many DCM rare variants, will enable DCM genetics to move into the mainstream of cardiovascular genetic medicine.

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Key Words: cardiomyopathy ■ genetic counseling ■ genetic testing ■ genetics.